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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,072	EYCKERMAN ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *9,10,12,14 and 17-21* is/are withdrawn from consideration.

5)☐ Claim(s) *22* is/are allowed.

6)☒ Claim(s) *1-8,11,13,15,16,22 and 23* is/are rejected.

7)☒ Claim(s) 2 is/are objected to.

8)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 5/6/05 has been entered in full. Claims 1, 3, 5, 6-8, 15 and 16 are amended. New claims 22 and 23 are added. Claims 9, 10, 12, 14 and 17-21 are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-8, 11, 13, 15, 16, 22 and 23 are under consideration in the instant application.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the EPO on 5/22/200. It is noted, however, that Applicants have not filed a certified copy of the 01202569.8 application as required by 35 U.S.C. 119(b).

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (2/8/2005).

The rejection of claims 1-8, 11, 13, 15 and 16 under 35 U.S.C § 112, second paragraph, at pg 5-6 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' amendments to claims 1.

The rejection of claims 1-8, 11, 13, 15 and 16 under 35 U.S.C. § 102(b) at pg 6-8 as being clearly anticipated by Nicholson et al, 2000, is *withdrawn* because the examiner improperly included these claims in the rejection.

As noted by Applicant at pg 6 of the 5/6/05, the rejection of claims 1-8, 11, 13, 15, and 16 under 35 U.S.C. 103(a) at pg 8-11 was withdrawn by the Examiner 3/22/05, as detailed in the Examiner-initiated interview summary of 3/22/05.

Please see new claim objections and rejections below.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 recites a recombinant receptor comprising an extracellular ligand-binding domain and a cytoplasmic binding domain. As the extracellular and cytoplasmic domains are on opposite sides of the cytoplasmic membrane, the receptor must be inherently be a transmembrane receptor. Therefore, the limitation of claim 2 that the receptor of claim 1 is a transmembrane receptor fails to further limit the parent claim.

Double Patenting

Claims 1-8, 11, 13, 15, and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7, 12, 14 and 16 of copending Application No. 10/303157 in view of U.S. Patent No. 5,885,779 and in further view of Nicholson et al, published June 6, 2000 (PNAS 97(12): 6493-6498). The basis of this provisional rejection for claims 1-8, 11, 13, 15, 22 and 23 is set forth at pg 2-5 of the 2/8/2005 Office Action. Claim 22 is newly included in this rejection.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Here, claim 1 of 10/303157 (amended 5/6/05) recites a receptor comprising an extracellular ligand binding domain and a cytoplasmic binding domain comprising a heterologous bait polypeptide, wherein said recombinant receptor is activated by binding of a ligand to said extracellular ligand binding domain and by binding of a prey polypeptide to said heterologous bait polypeptide. Claims 1 and 22 of the instant

application (amended 5/6/05) differs in that they encompass a receptor that is is inhibited by binding of a fusion protein polypeptide to the bait domain, wherein the fusion protein comprises a prey polypeptide and either a inhibitor of activation or a recruitment site for an inhibitor of activation. Other relevant claims of 10/303157 teach as follows: Claims 2-3 teach use of homomultimerizing or heteromultimerizing receptors in the recombinant receptor; Claims 4-5 and 7 of 10/303157 teach use of a bait that requires modification, such as phosphorylation, for binding of the prey molecule, and that the modification state is dependent on ligand binding; and claims 12 and 14 teach use of a vector encoding the recombinant and eukaryotic cells comprising the vector.

The specification of 10/303157 does not teach a receptor wherein the receptor is inhibited by binding of a prey polypeptide to the bait polypeptide.

U.S. Patent No. 5,885,779 teaches a yeast two-hybrid system wherein the interaction of the bait and prey molecules causes inhibition of a transcriptional activator to which the bait is fused. This system can be used to screen for molecules that disrupt the bait-prey binding and lead to transcriptional activation. 5,885,770 further teaches (column 3, starting at line 60) advantages of using a system that relies on activation of a reporter to indicate disruption of bait-prey interaction. Such a system avoids pitfalls of a system relying on loss of a signal to indicate bait-prey disruption, wherein "failure to obtain expression may be caused by factors other than interference with the protein-protein interaction of interest. For example, compounds that interfere with transcription may score a false positive result. Similarly, compounds that generally inhibit cell growth may score a false positive result by appearing to interfere with the expression of a reporter gene that would confer survival on a restrictive medium."

Nicholson teaches a protein, SOCS-3, which inhibits signaling of the cytoplasmic gp130 domain of a chimeric receptor by binding to the gp130 domain.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the cytoplasmic domain of a receptor such as gp130, which is inhibited by prey (SOCS-3) binding, for cytoplasmic domain of the receptor taught by 10/303157, which is activated by prey binding. The person of ordinary skill in the art would be motivated to do so because 5,885,779 teaches that screening for

compounds that disrupt protein-protein interactions is best achieved with a system that reduces false positives, and Nicholson teaches a receptor based system where disruption of the protein-protein interaction leads to activation. One would expect success because 10/303157 teaches a receptor where prey binding activates the receptor, and teaches its use for screening prey-bait binding interactions, and in the absence of other evidence, one would expect a screen using an inhibitor would work just as well because such systems have been developed for transcriptional based two-hybrid systems.

It would further have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the recombinant receptor as taught in claims 2-5 and 7 of 10/303157, to produce a receptor as taught by these claims but wherein the receptor is inhibited by binding of a prey molecule. The person of ordinary skill in the art would be motivated to include an inhibitor for the same reasons as discussed above and because the further teachings of claims 2-5 and 7 are modifications of the receptor that allow for versatility in the type of receptors or bait used, and one would have expected success because, in the absence of other evidence, a receptor that is inhibited by prey binding would work just as well with these modifications as a receptor that is activated by prey binding.

It would further have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the vectors or eukaryotic host cell as taught in claims 12, 14 and 16 of 10/303157, to produce a vector that encodes a receptor that is inhibited by prey binding, or a host cell comprising said vector. One would have been motivated to do so because of the motivation to produce a receptor that is inhibited by prey binding as described above, and because a vector and host cell is necessary to produce such a receptor, and one would have expected success because, in the absence of other evidence, such a vector or host cell would be expected to work just as well to produce a receptor inhibited by prey binding as a vector or host cell that produces a receptor that is activated by prey binding.

This is a provisional obviousness-type double patenting rejection.

The Examiner notes Applicants' statement at page 7 of the 5/6/05 response that Applicants defer substantive argument of the above provisional rejection. It is noted that the issue will become moot for the first of the two cases to be found allowable, see MPEP 804. However, Applicants are cautioned that any argument of the above rejections should not be delayed; argument of the double patenting rejection after prosecution has otherwise concluded will not be considered as being timely. The only actions that will be deemed appropriate at such time as claims are found otherwise allowable will be cancellation of claims or filing of a terminal disclaimer.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 16 was amended 5/6/05 to encompass a cloning vector encoding a recombinant receptor comprising a nucleotide sequence encoding the cytoplasmic binding domain wherein the nucleotide sequence comprises at least one restriction site configured to allow an in frame fusion of a nucleic acid sequence encoding the prey polypeptide, wherein insertion of the nucleic acid sequence encoding the prey polypeptide in the cloning vector results in the vector of claim 12. New claim 23 was presented 5/6/05 and is drawn to a vector of claim 11, further comprising a nucleotide that encodes the cytoplasmic domain, wherein the nucleotide sequence comprises at least one restriction site configured to allow an in frame fusion of a nucleic acid fragment that encodes the prey polypeptide. In the 5/6/05 response, Applicants do not indicate where in the specification that support for amended claim 19 or new claim 27.

Furthermore, the Examiner can find no reference or support in the specification as originally filed for a transmembrane receptor with a cytoplasmic domain with a prey polypeptide fused in frame. There is no conception in the specification of a recombinant receptor with a cytoplasmic domain fused to a prey polypeptide, nor does the concept of the specific recombinant receptor flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for the genus of molecules encompassed by amended claim 16 or new claim 23.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 1-8, 11, 13, 15, 16 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "a cytoplasmic binding of the receptor origin, wherein the cytoplasmic domain comprises a heterologous bait polypeptide, heterologous to the receptor." The phrase "a cytoplasmic binding domain of the receptor origin" indicates that the entirety of the cytoplasmic binding domain comes the receptor. Therefore, if the entirety of the cytoplasmic binding domain comes from the receptor, it is unclear how the domain can comprises "a heterologous bait polypeptide, heterologous to the receptor."

Claim 16 recites "a cloning vector encoding a recombinant receptor, comprising a nucleotide sequence encoding the cytoplasmic domain, wherein the nucleotide sequence comprises at least on restriction site configured to allow an in frame fusion of a nucleic acid fragment encoding said prey polypeptide; wherein insertion of the nucleic acid fragment encoding said prey polypeptide in the cloning vector results in the vector of claim 11". An in-frame fusion of a prey polypeptide and the cytoplasmic domain would result in a recombinant receptor with a prey polypeptide fused to the cytoplasmic domain. However, the vector of claim 11 encodes the recombinant receptor of claim 1 and the receptor of claim 1 does not have a prey polypeptide fused to the cytoplasmic

domain. Therefore, it is unclear how the vector of claim 18 can result in the vector of claim 12.

Claim 16 recites the limitation "the cytoplasmic binding domain" in line 3 and the limitation "said prey polypeptide" in line 5. There is insufficient antecedent basis for either of these limitations in the claim.

Claim 23 is indefinite because it recites "the vector of claim 11, further comprising a nucleotide sequence that encodes the cytoplasmic domain..." However, the vector of claim 11 encodes the recombinant receptor of claim 1, which includes a cytoplasmic domain. Therefore, because the language used in claim 27 suggests that the vector further comprises a cytoplasmic domain, it is unclear in claim 27 whether the vector encodes a single cytoplasmic domain or two cytoplasmic domains.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11, 13, 15, 16, 22 and 23 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Medici et al, 1997 (The EMBO Journal. 16(24): 7241-7249).

Namely, Medici teaches (page 7246 and Figure 6) a chimeric receptor composed of yeast STE2 transmembrane receptor and any Protein X that binds a Protein Y. This recombinant receptor comprises an extracellular ligand binding domain of a receptor origin (the STE2 receptor binds the extracellular ligand α-factor), a cytoplasmic binding domain of the receptor origin that comprises a heterologous bait polypeptide (the cytoplasmic region of the chimeric STE2 receptor includes the protein X). Furthermore, Medici teaches binding of a prey fusion polypeptide comprising Protein Y to the receptor. While Medici does not teach that the activation of said receptor is inhibited by binding of the prey fusion protein to said heterologous bait polypeptide, it is an inherent

characteristic of the receptor taught by Medici that if a prey comprising an inhibitor were to bind to the bait portion of the receptor, activation would be inhibited. Therefore, the receptor taught by Medici anticipates the limitations of the receptor of claims 1. Similarly, claim 3 recites a limitation that is an inherent characteristic of the recombinant receptor of Medici; if a prey comprising an inhibitor were to bind to the receptor, addition of a compound that disrupts the interaction would allow activation of the receptor. Claim 2 is also anticipated because STE2 is a transmembrane receptor.

The GPCR STE2 is known to form homomers and heteromers in vivo (Overton, et al, 2000. Current Biology. 10(6): 341-344. Cited here as an evidentiary reference only). Ste2 must also form a heteromeric complex with a Gα, Gβ and Gγ prior to activation of the receptor (see Medici, Figure 6). Therefore, the recombinant STE2 receptor taught by Medici clearly anticipates the further limitations of claims 4 and 5.

Medici further teaches (Materials and Methods, page 7248) vectors comprising the nucleic acid encoding the recombinant receptor and eukaryotic host cells (yeast) comprising the vector, which anticipates the further limitations of claims 11, 13 and 15.

New claim 22 encompasses a receptor with the same limitations as claim 1, and therefore is clearly anticipated by Medici for the same reasons as the receptor of claim 1.

New claim 23 is drawn to a vector of claim 12, further comprising a nucleotide sequence that encodes the cytoplasmic domain, wherein the nucleotide sequence comprises at least one restriction site configured to allow an in-frame fusion of a nucleic acid fragment that encodes the prey polypeptide. As described above, Medici teaches a receptor with all of the limitations of claims 1, and a vector encoding said receptor. Medici teaches (pg 7248) that the vector contains a restriction site for the in-frame fusion of a protein. The recitation of claim 27 of "to allow an in frame fusion of a nucleic acid of fragment that encodes the prey polypeptide" is interpreted as an intended use and bears no accorded patentable weight. Amended claim 16 is rejected on the same grounds as it encompasses a vector encoding a similar receptor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Medici et al, 1997 in view of Osborne et al, 1995 (cited by the Applicant in the IDS submitted 6/24/04).

Claim 6 as amended encompasses a recombinant receptor wherein binding of said prey polypeptide depends upon a modification state of said heterologous bait polypeptide. Claim 7 encompasses a modification state of phosphorylation. Claim 8 encompasses a receptor of claim 6 wherein the modification state depends upon binding of a ligand to the extracellular ligand binding domain.

The recombinant receptor taught by Medici is summarized above. Medici does not teach a recombinant receptor wherein binding of the prey polypeptide is dependent on the modification state of said heterologous bait polypeptide.

Osborne (page 1474) teaches "protein-protein interactions are often dependent on the post-translational modification of one component of the complex." Osborne further teaches that IgE receptor activation leads to phosphorylation of the cytoplasmic domain of the receptor. Osborne further teaches a modified yeast two-hybrid system in which a kinase is co-expressed with the bait molecule, so that the bait molecule is phosphorylated, and prey molecules that interact with the phosphorylated bait are detected.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the recombinant receptor taught by Medici to include a bait polypeptide, such as the cytoplasmic domain of an IgE receptor, that is phosphorylated, as taught by Osborne. The person of ordinary skill in the art would have been motivated to make that modification because Medici teaches (page 7247)

the advantage their recombinant receptor can be used as a two hybrid system to investigate protein-protein interaction on the cytoplasmic side of the cell membrane. One would have expected success because in the absence of other evidence, the yeast two-hybrid system taught by Medici would be expected to work as well as the one taught by Osborne.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bridget E. Bunner

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PATENT EXAMINER